PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Single use versus reusable catheters in intermittent CatheterizatiOn for treatment of urinary retention: a protocol for a Multicenter, Prospective, RandomizEd controlled, non-inferiority trial (COMPaRE)
AUTHORS	van Doorn, Tess; Berendsen, Sophie; Scheepe, Jeroen; Blok, Bertil

VERSION 1 – REVIEW

REVIEWER	Mitchell, Brett The University of Newcastle, School of Nursing and Midwifery
REVIEW RETURNED	24-Oct-2021

GENERAL COMMENTS	Thank you for the opportunity to review this protocol paper. This is a very worthy topic, one where there is little evidence and wide clinical variation. The topic is vitally important to patients/consumers. Introduction Good background to the issues and importance of this topic. Line 23: reference to Canada and Australia. This makes it seem like reusable catheters are the norm. That is not necessarily true. There is variation of both CISC and reusable. Line 31 – Prieto study. I would not make reference to this study, it was redacted/withdrawn from publication by Cochrane in 2017. Methods Great to see consumer co-design. Randomisation: can you please provide a little more detail on how the ALEA approach will be used on conjunction with stratification? Blinding: this needs to be discussed. Intervention arm: Can you please provide the active ingredients and concentration of the Milton solution? Control arm: While I understand the need for patient preference, the variation in different catheters may be an issue. Trial objective: The term 'not less safe and not less efficient' – the latter is difficult to line up against a specific outcome. "Not less safe" is presumably assessed against the primary outcome of sUTI. How is 'not less efficient' evaluated against a specific outcome? Explanation of some of the secondary outcomes is required. E.g. Changes in urine cultures. How will this be undertaken? What is the outcome for this? Recommendations are debatable as to whether they are an outcome. They are an output. Might a table outlining the primary and secondary objective against specific outcomes be useful? Line 53: no need for the word 'these'

	Outcomes: I think these needs to be strengthen or further justified. sUTI: this is a very simplistic definition. E.g. according to this, delirium (with no urine culture or dipslide etc) would constitute a sUTI. Most internationally recognised sUTI definition would require more than one of the criteria listed e.g. NHSN definitions. Bacteremic UTI: this is essentially asymptomatic bacteriuria. There will be questions raised in main result paper about the utility of such a definition. The paper and significance of any results for a change in practice would be strengthen considerably if the primary outcome included both symptoms and microbiological confirmation. What I am concerned about is whether, if the results illustrated no difference, this would result in a change of practice given the outcomes used. What will be the threshold for willingness to pay in the cost effectiveness analysis? This is important in the context of the perspective taken and how will be paying. Will data and costs on GP visits or hospitalisation be captured? If so, what method will be used to determine costs for each of these? Sample size: Not previous comment about Prieto and withdrawl. While the withdrawl may not be related to the issue relevant to the sample size calculation, perhaps papers from the Prieto review could be used or referred to in addition. I would like to see a sample size calculation refers to the primary outcomes and anticipated incidence. Further information analysis is required, specifically how the incidence of sUTI will be compared and out any other variables will be included and accounted for e.g. type of catheter used in the control arm; other issues that may effect the primary outcome (particularly if it continues as defined at present). The CE analysis section could go in this section if the author or editors wished. How will variation in individual practice be recorded? E.g. technique? Noting that a lubricant is part of the intervention arm (catheter), how will data on lubricants in the control arm be recorded and accounted for? At present, just for argument sake, if no lubricant was used in the control arm, how would we know whether it was the catheter or lubricant that was responsible for any (non) effect? The schedule talks about a patient diary. In the intervention section, I would like to see some of this detail included i.e. demonstrating that you can evaluate or measure individual compliance with the intervention. Discussion Line 12: “up until now” Thank you again for getting this study funded and preparation of this protocol. I support publication of this protocol, but I hope the additional comments above strengthen it further. I would like to see some clearer evidence on this topic, it is needed.

REVIEWER	Lavelle, John Stanford University, Urology

REVIEW RETURNED	02-Nov-2021

GENERAL COMMENTS	1. The uroweb.org URLs in the references 3, & 8 need to be corrected, 2. Reference 13, needs to be completed for vol, page numbers. 3. In the background: Are there reasons for why the use of disposible catheters in the Netherlands inceased so much? For example in the US, following the IDSA guidlines on Catheter associated UTI's were it was pointed out that the FDA only approved catheters for single use, the use of catheters dramatically increased in the US following changes in CMS regulations shortly afterwards. 3. The section from page 7 ln18 - 47 may need to be revised, as the reason for Prieto JA Cochrane Review withdrawal was due to errors in the analysis, while this is aknowledged in the section, perhaps these references could be updated. 4. How do you plan to seperate, spontanous urolithiasis formation, from that associated with bacteriuria? As this same section (pg7 lns17-47) suggests, that 'unwanted bacterial contamination" leads to stone formation as a complication. Interpretation of this section could be made several ways a) resuse intermittent catheterization leads to 'unwanted bacterial contamination' which is complicated by urinary stone formation and symptomatic UTIs' b) In the early stages of SCI / immobility, there is an increase in hypercalcuria which may also lead to stone formation - is this accounted for in the trial design c) There are some individuals who have a metabolic recurrent stone issue, who may be stone free at the beginning of the study. Is this specifically excluded in the exclusion criteria , or is it just subjects who currently have a urinary stone. d) It is usually assumed that individuals who are cathing have asymptomatic bacteriruia, is there evidence to support the suggestion that subjects performing intermittent catherization with new catheters each time, in clean conditions, have sterile urine? (compared to reuse catheterization) 5) Historically, when intermitent catheterization was introduced in the 1970's and earlier, there was less concern about UTI's what is the data from this era? It should be in the background. 6) What is the potential for recyclinng the current intermittent catheter materials? 7) In the Methodology, please define the nature of the help recieved from the CISC patients? Where other groups included and if not why not? The chronic Catheterization group who preveiously perhaps performed CIC may have some valuable insight to help with adherence with CIC as is the stated objective of this part of the study. 8) In the inclusion criteria, Do the subjects have to perform the CIC themselves or may it be administered by an appropriate care giver - If so, please so state specifically. 9) Given that the subjects may be recruited 2 weeks following initiation of CIC, do the investigators think that this will be enough experience fot the subjects? Is there any evidence to support for or against this timeline? 10) Please provide compete details as to how the ALEA randomisation process will work and provide the company reference as needed. 11) Is the radomization pattern made prior to the study? if so / not, how will the pattern be administered at the various study sites?

	What precautions will the process have? Will there be any weighting of the radomised groups? 12) What are the sizes and types of catheter material to be used in the intervention arm for both the cliny and purecath catheters? 13) What is the CE notifying body number and certification validiity period for each product (should cover the expected duration of the trial).? 14) Please include the trial begining and projected end dates for recruitment 15) What is the precise dilution of Milton to be used in the study? 16) What is the evidence that Milton is a safe agent to use in the urinary tract? While it might be save to use in baby bottles, diluted in a lot of formula / milk, this referee is not sure that bleach is a good material to have in the urethra, and potentially could provide entry to bacteria if it damages the urethral or bladder epithelium and thus promote UTI and thus bias the study. 17) Please provide details on the subject training for the Cliny and Purecath products. 18) Will there be a standard protocol throughout for all subjects performing CIC or if there are different protocols how will this be handled statistically? 19) The control arm subjects will be allowed to use their choice of catheter (presumably these will be of different materials (e.g latex, rubber, silicone, PVC, etc) +/- their choice of lubicrant, or prelubricated depending on the catheter used. Does this not produce confounding groups statistically, as the two catheter types in the intervention arm vs. several (as yet unknown) in the control arm. How is this to be handled statistically? 20) Please provide a definition of "safe" for the primary objective or do you mean: To determine that the incidence of symptomatic UTIs in subjects who use reuasble intermitent urinary catheters is not significantly greater than subjects who use single use intermitent urinary catheters, or are you trying to introduce the concept of 'safe' include your secondary objectives of admissions, or urethral trauma, stone fromation etc. at the same time, which would be statistically problematic? 21) Are UTIs to be based on use of a dipstick / slide assessment of urine? 22) Is there allowance for definition of the UTI site - cysitis vs pyelonephritis, What is to happen if subject has prostatitis or epididymitis? Do these count? 23) With blood stream infections, does the urinary pathogen have to match between the blood and urine to definine the source as the urinary tract? 24) A chart of the subject visits and procedures at each visit would be useful to provide a clear timeline for he study protocol. 25) What happens if a subject is admitted to another hospital (outside of the study centers for example) and diagnosed with a UTI that does NOT meet study criteria? 26) What happens if a subject has a significant complication e.g sepsis from an obstructing upper tract stone, and has an indwelling urinary catheter placed for monitoring / treatment? 27) Similar to 25 & 26 in the case of new onset urethral false passage or stricture formation. 29) Similar to above - what happens in situation where patient is admitted to hospital or has a significant other non urological emergency? 30) The Qol questionnaires: Please provide references to the Dutch language validation studies and aknowledgement that the

	relevant propriatory permissions have been obtained. The referee assumes the questionnaires will be administered in the Dutch language, if not please so state (and in what language they will be administered). 31) Is there an independent data montioring group / board? If so, how often will they meet and will they be provided with regular updates of the study progression? 32) How will the data collection be managemed? Paper CRF's or an online CRF? 33) How will the collected data be monitored for completeness and what will be the process for obtainining incomplete data (and the relevant timeline) 34) How will the study process statistically incomplete data? 35) What are the expected limitations or possible problems of the study? 36) On the trial registration site, the start date is recoreded as 202-01-19, yet the consort checklist the recruitment question is not answered (item 14a) Please explain 37) In evaluating the interventional catheter products, this referee could only find these items on Austrialian websites, Are they actually approved in the EU? or widely used in the EU? or just being imported for the study? If so, please state. (It is recognised that the CE mark means the the manufacturing process(es) meet EU standards). If not actually approved for EU use, please advise that the appropriate regulatory paperwork is submitted and approved. 38) Does the supplier or manufacturer of any of the study products have any contribution / inlfuence / consultation to this study or study personnel in the broadest sense? If so, please so state, if this is positive, please explain the conflict mitigation process..If not, please so state. 39) Are there any stopping points for the study? If there is no data monitoring board, are the investigators going to examine the study data at intermittent defined points for safety so the trial would be stopped if there sre marked differences between the intervention arm vs the control arm of the study. If there is such a review process, please so state, and also specify the study stopping point / criteria.

REVIEWER	Welk, Blayne Western University
REVIEW RETURNED	06-Nov-2021

GENERAL COMMENTS	The authors have taken on a significant gap in the urologic literature, and aim to conduct a large RCT to determine if there is a difference in single use versus reuse catethers for lower urinary tract dysfunction. This is a well throught out study. A few comments are included below to include some additional important details in this protocol manuscript. A few points below for the authors to consider: 1. Some minor grammatical issues are located throughout the article. For example: Abstract, introduction: …"power is performed" should be "power has been performed". Background, 2nd sentence: needs to be rephrased: Urinary retention or significant urinary retention is due to LUTD, which can be caused by SCI/MS or in some cases it can be idiopathic. Discussion, 1st sentence: "Up to know" should be "Up to now".

	2. Two of the objectives do not have any associated methodology reported: explore patients perspectives on reuse seems like it should need a brief summary of a qualitative interview process for some participants at the end of the study. Similarly, determine whether urine cultures change seems like it would require a regular urine sample at study start and end, and some discussion of microbiome analysis etc. 3. What catheter type would generally be used by the control population? I would worry that different catheter types (esp with the discussion of a special non-lubricated catheter for the intervention group) may be a cointervention which could decrease the primary/secondary outcomes? If these are special catheters designed to be reused, that should be made clear so that readers understand it is not a study of reuse of regular PVC catheters (which makes the generalizability of the results a bit more challenging to third world countries etc). 4. The SF Qualiveen is designed for the neurogenic population. Is there a plan to validate within non neurogenic CIC users, or conduct analysis of this specifically within the neurogenic subgroup? 5. How will antibiotic use be adjusted for in the study (ie low dose prophylaxis, multiple courses of antibiotics during which the patient will not be at risk for the primary outcome)? 6. Some more details about the collection of the primary outcome would be helpful. This will be critical to the trial success, and one of the hardest things to do in long-term UTI studies. In figure 1, you are only in contact with them every few months by telephone. How do you know when they have a UTI? How will you make sure symptoms are fully documented? How will you ensure that urine cultures are done for all patients, and people aren't treated on spec with antibiotics by non-trial physicians? Are the trial staff on call 24/7 to assess a sUTIs for these patients throughout the trial? 7. Is the analysis going to be per protocol (as is usually done for noninferiority)? I would assume some people with frequent UTIs in the reuse arm will want to switch over to single use, how will their data be analyzed? 8. How will adverse events be collected? Only if patient reports them, or will there by active screening for them (ie renal and bladder US at the end of the study to assess for stones)? 9. Are patients reimbursed for any expenses/participation in the study? If so this should be specified in the protocol. 10. What are the actual/expected start date and estimated end date of the study? 11. The statistical analysis of a non-inferiority trial is a bit more complex, and I think this should be fully described in the statistical methods section. Furthermore, the outcome will be a non-independent, repeated event over time, which adds another layer of complexity that should be addressed.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Prof. Brett Mitchell, The University of Newcastle Comments to the Author:
Thank you for the opportunity to review this protocol paper. This is a very worthy topic, one where there is little evidence and wide clinical variation. The topic is vitally important to patients/consumers.

Introduction
Good background to the issues and importance of this topic.
Line 23: reference to Canada and Australia. This makes it seem like reusable catheters are the norm. That is not necessarily true. There is variation of both CISC and reusable.
Authors' response: Thank you for your comment. We are aware that single use catheters are also used in Canada and Australia and we agree that the sentence implies that this is not true. We therefore changed the sentence into the following: "In the Netherlands, virtually all patients on CISC utilize single use (=disposable) catheters, which is in contrast to several high income non-European countries like Japan, Canada and Australia. In those countries, single use and reusable catheters are both used for CISC."

Line 31 – Prieto study. I would not make reference to this study, it was redacted/withdrawn from publication by Cochrane in 2017.
Authors' response: We thank you for this advice and we changed our references to the updated Cochrane analysis of 2021.

Methods
Great to see consumer co-design. Randomisation: can you please provide a little more detail on how the ALEA approach will be used on conjunction with stratification?
Authors' response: Upon randomization, patients will be allocated a unique study subject number in chronologically ascending order for every study site, starting with 1 (for example Erasmus MC : EMC001). They will be randomized to the intervention arm (reusable catheter) or control arm (single use catheter). There will be five stratification factors: hospital, cause for catheterization (levels: neurogenic, non-neurogenic), age (levels: 16-17, 18-49, >=50), gender (levels: male, female), and the female patient group will be balanced for pre- and post-menopausal status (levels: pre-menopausal, menopausal, post-menopausal). There is not a pre-specified list upon randomization, but each combinations of stratification factors will form a combination. Within each combination, ALEA will randomly assign a study arm. The rational for this approach is that it will maximize the probability of assigning a new participant in the study arm with the lowest number of patients. The company for the randomization procedure is the Clinical Trial Center of the Erasmus MC. We have added this information in the manuscript in the paragraph 'Recruitment and randomization'.

Blinding: this needs to be discussed.
Authors' response: We have added the following sentences on the blinding of study participants and research staff. 'Blinding of the study participants and clinical research staff is impossible due to the different appearances and conditions of the disposable catheters and reusable catheters for CISC. The statistician involved, will be blinded for the intervention and control group during the analysis.'

Intervention arm: Can you please provide the active ingredients and concentration of the Milton solution?
Authors' response: The active ingredient of the Milton solution is sodium hypochlorite 2% and will be diluted with cold tap water (1:80). The manufacturer of the reusable catheter tested the compatibility of diluted sodium hypochlorite 2% solution with the reusable catheters. We have added this information to the paragraph "Intervention arm".

Control arm: While I understand the need for patient preference, the variation in different catheters may be an issue.
Authors' response: Our aim is to compare the reusable catheter to the standard care provided in the Netherlands. Allowing for different types of single use catheter and several other material uses may increase unexplained variation in sUTI in the control arm, and potentially a loss of power. Defining a rigid treatment protocol for the control arm would remove this unexplained variation, but we expect that the ability to recruit patients for the control arm would be much harder. Our aim is to include 228 patients in the control arm, so we would expect to get a good representation of contemporary clinical practice in the control arm.

Trial objective: The term 'not less safe and not less efficient' – the latter is difficult to line up against a specific outcome. "Not less safe" is presumably assessed against the primary outcome of sUTI. How is 'not less efficient' evaluated against a specific outcome? Explanation of some of the secondary outcomes is required. E.g. Changes in urine cultures. How will this be undertaken? What is the outcome for this? Recommendations are debatable as to whether they are an outcome. They are an output. Might a table outlining the primary and secondary objective against specific outcomes be useful?
Authors' response: We agree with the reviewer that some of the secondary outcomes are difficult to line up against the objectives or are not clearly described. We made use of his suggestion to include a table with all objectives and the primary and secondary outcomes (see below).
At first, our primary objective is to determine whether reusable catheters are not less safe as single use catheters. This is measured by our primary outcome: symptomatic UTIs. Other secondary outcomes are also used to investigate the safe use of the reusable catheters compared to single use catheters, such as the amount of hospitalization due to a sUTI, the amount of bacteremic UTI, urethral damage leading to clinical significant strictures, clinical significant kidney- or bladder stone formation and episodes of macroscopic hematuria.
The efficiency of the reusable catheters compared to the single use catheters is measured by patient reported outcome measures (PROMs) on urinary symptoms (SF-Qualiveen), patient satisfaction (ISCQ, InCaSaQ, PGI-I) and QoL (EQ-5D-5L). The cost-effectiveness of the reusable catheter will be calculated on the basis of PROMs (iMCQ, iPCQ, EQ-5D-5L) and hospital records and will be expressed in QALYs. We agree that the fourth objective to determine whether reuse of catheters leads to changes of the urine cultures is debatable. We removed bacteriuria as a secondary outcome, as this is output rather than an outcome.

Line 53: no need for the word 'these'
Authors' response: Thank you for this remark. We have deleted 'these'.

Outcomes: I think these needs to be strengthen or further justified. sUTI: this is a very simplistic definition. E.g. according to this, delirium (with no urine culture or dipslide etc) would constitute a sUTI. Most internationally recognised sUTI definition would require more than one of the criteria listed e.g. NHSN definitions.
Authors' response: Our apologies if our definition of a sUTI was not clear. In our protocol a symptomatic UTI is defined as clinical signs and symptoms of a UTI with the presence of bacteriuria. We choose to define bacteriuria by a positive nitrite test, positive dipslide, positive urine sediment or a positive urine culture (a urine culture is positive according to the protocol of the medical microbiology and infection diseases department of the participating hospital). Study participants may consult their general practitioner during the study follow-up and these different diagnostic tests are used by general practitioners to diagnose bacteriuria/sUTI. During the follow-up visits, we will assess any clinical signs and symptoms of the study participants and we will request the results of any diagnostic tests performed at the hospital or at the general practitioner. On the basis of this, we assess whether the study participants have undergone a sUTI as defined in our protocol. We have changed the text in the

protocol to clarify our definition of sUTI under the paragraph ‘Primary Outcome Measure’.

Bacteremic UTI: this is essentially asymptomatic bacteriuria. There will be questions raised in main result paper about the utility of such a definition.
Authors’ response: We have clarified our definition of a bacteremic UTI in our protocol. The definition is a sUTI and a blood culture positive for a known uropathogen, providing that their urine culture matches the positive blood culture (in case a urine culture was taken before receiving antibiotics).

The paper and significance of any results for a change in practice would be strengthen considerably if the primary outcome included both symptoms and microbiological confirmation. What I am concerned about is whether, if the results illustrated no difference, this would result in a change of practice given the outcomes used.
Authors’ response: As clarified above, our definition of a sUTI is based on clinical signs + microbiological confirmation. General practitioners are advised to perform an urine culture. In an ideal setting we would like to see microbiological confirmation by urine culture in every patient, but in practice, and therefor also in this protocol, an urine dipslide, dipstick or sediment is also accepted.

What will be the threshold for willingness to pay in the cost effectiveness analysis? This is important in the context of the perspective taken and how will be paying. Will data and costs on GP visits or hospitalisation be captured? If so, what method will be used to determine costs for each of these?
Authors’ response: We will use a willingness to pay (WTP) threshold of €20,000/QALY. Which is based on the reference value for cost-effectiveness that is determined by the National Health Care Institute of The Netherlands. A study on health-economic burden of catheter-associated UTI in England used a similar WTP threshold of £20,000/QALY based on the NICE guidelines. The cost-effectiveness analysis will be performed by the institute for Medical Technology Assessment (iMTA) of the Erasmus University Rotterdam (EUR). They are specialized in cost-effectiveness analyses and have developed Dutch questionnaires to measure the total health care costs consumption of every study participant. These questionnaires also answers questions about health care professional visits, hospitalization, treatments and the use of medication. We have added the above information (including references) in the paragraph ‘Cost-effectiveness analysis’.

Sample size: Not previous comment about Prieto and withdrawl. While the withdrawl may not be related to the issue relevant to the sample size calculation, perhaps papers from the Prieto review could be used or referred to in addition. I would like to see a sample size calculation refers to the primary outcomes and anticipated incidence.
Authors’ response: We are aware that Cochrane analysis of Prieto was retracted. The heterogeneity of the current trials makes it difficult to calculate a reliable sample size. This is a pitfall, but unfortunately these are the best numbers on which a sample size can now be based. The sample size calculation is performed by a statistician and checked by the Medical Ethical Committee of the Erasmus MC. Figure 2 of the abridged version of the Cochrane analysis of Prieto shows which studies are performed and used for this sample size calculation (Pachler et al. (1999), Sutherland et al. (1996), Leek et al. (2013), Schlager et al. (2001), Moore et al. (2013), Duffy et al. (1995), King et al. (1992).

Further information analysis is required, specifically how the incidence of sUTI will be compared and out any other variables will be included and accounted for e.g. type of catheter used in the control arm; other issues that may effect the primary outcome (particularly if it continues as defined at present). The CE analysis section could go in this section if the author or editors wished.
Authors’ response: As discussed previously, we are aware that the variation in different catheters may play a role in our outcome measures. In this study design, we deliberately chose for patient preference in the control group, as we wanted to compare the reusable catheter with the current clinical practice in the Netherlands.

How will variation in individual practice be recorded? E.g. technique?
Authors' response: Any variation in individual practice and technique will be registered during the follow visits by standardized questions in the pre-designed case report forms (CRFs).

Noting that a lubricant is part of the intervention arm (catheter), how will data on lubricants in the control arm be recorded and accounted for? At present, just for argument sake, if no lubricant was used in the control arm, how would we know whether it was the catheter or lubricant that was responsible for any (non) effect?
Authors' response: At every visit, all study participants (intervention and control group) are asked if they used lubricant with their catheters. Our aim is to compare the reusable catheter to the standard care provided in the Netherlands. We will register all type of catheters used by the study participants (also pre-baseline for the intervention group), so we would expect to get a good representation of contemporary clinical practice in the Netherlands.

The schedule talks about a patient diary. In the intervention section, I would like to see some of this detail included i.e. demonstrating that you can evaluate or measure individual compliance with the intervention.
Authors' response: during the follow-up visits individual compliance will be evaluated (including adherence to the cleaning procedure and the amount of catheterizations performed with the reusable catheter).

Discussion
Line 12: "up until now"
Authors' response: Thank you for this remark. We have changed 'know' into 'now'.
Thank you again for getting this study funded and preparation of this protocol. I support publication of this protocol, but I hope the additional comments above strengthen it further. I would like to see some clearer evidence on this topic, it is needed.

Reviewer: 2 Prof. John Lavelle, Stanford University
Comments to the Author:
1. The uroweb.org URLs in the references 3, & 8 need to be corrected, 2. Reference 13, needs to be completed for vol, page numbers.
Authors' response: We have updated all references.

3. In the background: Are there reasons for why the use of disposable catheters in the Netherlands inceased so much? For example in the US, following the IDSA guidlines on Catheter associated UTI's were it was pointed out that the FDA only approved catheters for single use, the use of catheters dramatically increased in the US following changes in CMS regulations shortly afterwards.
Authors' response: It is very likely that the large increase in usage of disposable catheters is worldwide accepted in countries where this is fully reimbursed. Our study in Neurourology and Urodynamics (ref 7) points to several possible contributing factors. First, the ageing population remains longer independent, and CIC can still be performed at old age. The number of users in the older population increased substantially. This explains only part of the observed increase in CIC users, as users increased in every age category. A second additional important explanation is the adaptation of the recommendation of the preferred use of single use CIC for urinary retention in all professional guidelines of urologists and rehabilitation physicians. Third, (temporarily) CIC use for dilatation of urethral strictures might became more common in ageing men. Another fourth explanation is the ongoing development of single use catheters resulting in higher usability.

3. The section from page 7 ln18 - 47 may need to be revised, as the reason for Prieto JA Cochrane Review withdrawal was due to errors in the analysis, while this is acknowledged in the section,

perhaps these references could be updated.
Authors' response: Thank you for this advice. We have changed this reference into the updated Cochrane review of 2021.

4. How do you plan to seperate, spontanous urolithiasis formation, from that associated with bacteriuria? As this same section (pg7 lns17-47) suggests, that 'unwanted bacterial contamination" leads to stone formation as a complication. Interpretation of this section could be made several ways
a) resuse intermittent catheterization leads to 'unwanted bacterial contamination' which is complicated by urinary stone formation and symptomatic UTIs'
Authors' response: We fully agree that unwanted bacterial contamination may lead to stone formation as a complication, but we are not able to make this distinction.

b) In the early stages of SCI / immobility, there is an increase in hypercalcuria which may also lead to stone formation - is this accounted for in the trial design
Authors' response: This is not accounted for in this trial, early staged institutionalized SCI patients are not included in this study.

c) There are some individuals who have a metabolic recurrent stone issue, who may be stone free at the beginning of the study. Is this specifically excluded in the exclusion criteria , or is it just subjects who currently have a urinary stone.
Authors' response: Subject who currently have a urinary stone are excluded. A metabolic recurrent stone disease is not an exclusion criteria.

d) It is usually assumed that individuals who are cathing have asymptomatic bacteriruia, is there evidence to support the suggestion that subjects performing intermittent catherization with new catheters each time, in clean conditions, have sterile urine? (compared to reuse catheterization)
Authors' response: We do not think that patients using disposable catheters have sterile urine. The current scientific literature shows that almost every patient on CISC has bacteriuria. Therefore, we agree that the fourth objective to determine whether reuse of catheters leads to changes of the urine cultures is debatable and removed this objective.

5) Historically, when intermitent catheterization was introduced in the 1970's and earlier, there was less concern about UTI's what is the data from this era? It should be in the background.
Authors' response: Concerns about UTIs in people with urinary retention were also there in the 1970s and earlier. It is precisely this that has led to CIC becoming a standardized treatment. The only alternative patients had was a chronic indwelling catheter or an external condom catheter, which both give a higher risk on developing a sUTI or other complications in comparison to CIC. This is the reason that no concerns were made for the fact that catheters were reused multiple times.

6) What is the potential for recycling the current intermittent catheter materials?
Authors' response: Looking at sustainability in the health care sector, the 10-R principles (levels of circularity) are often used to estimate the impact on the environment and are ranked from the highest impact (Refuse; refuse the use of raw materials) to lowest impact (recover; incinerate waste with energy recovery). Reuse is the fourth highest method to make an impact on the environment, while recycle is the next-lowest. Our opinion is that recycling can make an difference, but that the use of a reusable catheter can have a much higher impact on the environment than recycling the plastic medical waste single use catheters generate.
In addition, most catheters are made of PVC or silicone, which usually has to be sent to different specialized recycling company to be properly recycled. In order to be able to recycle intermittent catheters, the medical material will therefore have to be collected centrally, which is a major logistic operation. This is the reason why (most) silicone / PVC (especially medical) products are not recycled and end up in the waste stream.

7) In the Methodology, please define the nature of the help recieved from the CISC patients? Where other groups included and if not why not? The chronic Catheterization group who preveiously perhaps performed CIC may have some valuable insight to help with adherence with CIC as is the stated objective of this part of the study.
Authors' response: Several chronic CISC patients were asked to advice on the design of the reusable catheter (e.g. material, flexibility, holder with cap) after viewing and holding the reusable catheter. Based on their feedback, it was decided to use the reusable catheter sets of CreateMedic and to have several PROMs completed during baseline and follow-up visits regarding the ease of use of the different type of catheters used in this trial. We have added this to paragraph 'Patients and public involvement statement'.

8) In the inclusion criteria, Do the subjects have to perform the CIC themselves or may it be administered by an appropriate care giver - If so, please so state specifically.
Authors' response: Study participants have to perform CIC themselves. Patients who are catheterized by a care giver are excluded for this trial. We wanted to ensure that the risk of bacterial contamination by others is as low as possible.

9) Given that the subjects may be recruited 2 weeks following initiation of CIC, do the investigators think that this will be enough experience for the subjects? Is there any evidence to support for or against this timeline?
Authors' response: Our clinical experience is that patients have mastered catheterization within two weeks. We also collect the date on which the patient started CIC, so beginners can be compared to more experienced users. Every participant enrolled thus far, has a minimum experience of 8 months (N=103).

10) Please provide complete details as to how the ALEA randomisation process will work and provide the company reference as needed.
Authors' response: Upon randomization, patients will be allocated a unique study subject number in chronologically ascending order for every study site (for example Erasmus MC: EMC001). They will be randomized to the intervention arm (reusable catheter) or control arm (single use catheter). There will be five stratification factors: hospital, cause for catheterization (levels: neurogenic, non-neurogenic), age (levels: 16-17, 18-49, >=50), gender (levels: male, female), and the female patient group will be balanced for menopausal status (levels: pre-menopausal, menopausal, post-menopausal). There is not a pre-specified list upon randomization, but each combinations of stratification factors will form a combination. Within each combination, ALEA will randomly assign a study arm. The rational for this approach is that it will maximize the probability of assigning a new participant in the study arm with the lowest number of patients. The company for the randomization procedure is the Clinical Trial Center of the Erasmus MC. We have added this information in the manuscript in the paragraph 'Recruitment and randomization'.

11) Is the randomization pattern made prior to the study? if so / not, how will the pattern be administered at the various study sites? What precautions will the process have? Will there be any weighting of the randomised groups?
Authors' response: see the answer above.

12) What are the sizes and types of catheter material to be used in the intervention arm for both the cliny and purecath catheters?
Authors' response: all reusable catheters are made of silicone and are uncoated.
Male version: Cliny catheter, Length 395 mm, 12FR, nelaton tip
Cliny catheter, Length 395 mm, 14FR, nelaton tip
Cliny catheter, Length 300 mm, 12FR, Tiemann tip

Female version: Cliny catheter, Length 165 mm, 12FR, nelaton tip
PureCath, Length 125 mm, 12FR, nelaton tip
PureCath, Length 125 mm, 14FR, nelaton tip

13) What is the CE notifying body number and certification validiity period for each product (should cover the expected duration of the trial).?
Authors' response: The manufacturer CreateMedic is certified to produce medical devices up to class 2B according to the European directives. This certificate is valid until 24th may 2024 and was authorized by SGS Belgium NV, Notified body 1639. All products manufactured by CreateMedic are covered by this certificate. We have uploaded the CE-certificate and a declaration of conformity for all products listed/produced by CreateMedic as a supplementary file.

14) Please include the trial beginning and projected end dates for recruitment
Authors response: Inclusion started at 20/02/2020 and the estimated end date for recruitment is 31/12/2023.

15) What is the precise dilution of Milton to be used in the study?
Authors' response: The active ingredient of the Milton solution is sodium hypochlorite 2% w/w and will be diluted with cold tap water (1:80). We have added this information to the paragraph "Intervention arm".

16) What is the evidence that Milton is a safe agent to use in the urinary tract? While it might be save to use in baby bottles, diluted in a lot of formula / milk, this referee is not sure that bleach is a good material to have in the urethra, and potentially could provide entry to bacteria if it damages the urethral or bladder epithelium and thus promote UTI and thus bias the study.
Authors' response: Unfortunately, no clinical data is available on the safe use of 0.6% diluted sodium hypochlorite 2% w/w solution, as no proper trial has been performed until thus far with a catheter specially designed for reuse. The manufacturer tested the compatibility of diluted sodium hypochlorite 2% w/w solution with the reusable catheters and advises to use a 0.6% dilution of sodium hypochlorite 2% w/w solution. This is already used for years in Australia for the purpose of cleaning the reusable catheter set. Sodium hypochlorite is also used for other purposes such as the prevention of central venous catheter-related infections (PMID: 30955154, PMID: 17099304), disinfecting root canal systems in endodontic treatments (PMID: 16989370), or as nasal lavage for the treatment of S. Aureus persistent rhinosinusitis (PMID: 18444487). In all cases (some with a concentration level of 10% sodium hypochlorite), is it confirmed to be safe.
The risks possibly associated with sodium hypochlorite, if used for the purpose intended in this trial, are skin or urethral irritation. We will collect all clinical data to establish if these risks occur. To minimize the risk on urethral/skin irritation in the intervention group, patients are advised to rinse the reusable catheter thoroughly with tap water before catheterization for the in- and outside of the catheter.

17) Please provide details on the subject training for the Cliny and Purecath products.
Authors' response: First, patients receive an explanation by telephone about the study design and the reusable catheter. If patients are still interested, an comprehensive patient information folder and an instruction video of the reusable catheter will be sent by email to all eligible patients. After a minimum of one week, patients are telephoned again to ask if they have any additional questions/remarks. When questions are answered and a patient is still interested in participation, a clinical visit is scheduled to demonstrate the reusable catheters. If the researcher (M.D. or research nurse) is convinced that the patient understands what participation entails, they will proceed to signing the informed consent form and randomization. If randomized to the intervention group, the study participant receives a flyer which demonstrates the cleaning steps of the reusable catheter. The reusable catheters will be ordered and delivered by the patients home in one week. After receiving the

reusable catheters, study participants receive an additional phone call to check if they feel confident to start with the reusable catheter. We have added this information under the paragraph ‘Follow-up and study procedures’.

18) Will there be a standard protocol throughout for all subjects performing CIC or if there are different protocols how will this be handled statistically?
Authors’ response: all data will be analyzed per-protocol and intention-to-treat.

19) The control arm subjects will be allowed to use their choice of catheter (presumably these will be of different materials (e.g latex, rubber, silicone, PVC, etc) +/- their choice of lubicrant, or prelubricated depending on the catheter used. Does this not produce confounding groups statistically, as the two catheter types in the intervention arm vs. several (as yet unknown) in the control arm. How is this to be handled statistically?
Authors’ response: our aim is to compare the reusable catheter to the standard care provided in the Netherlands. Allowing for different types of single use catheter and several other material uses may increase unexplained variation in sUTI in the control arm, and potentially a loss of power. Defining a rigid treatment protocol for the control arm would remove this unexplained variation, but we expect that the ability to recruit patients for the control arm would be much harder. Our aim is to include 228 patients in the control arm, so we would expect to get a good representation of contemporary clinical practice in the control arm.

20) Please provide a definition of "safe" for the primary objective or do you mean:
To determine that the incidence of symptomatic UTIs in subjects who use reuasble intermitent urinary catheters is not significantly greater than subjects who use single use intermitent urinary catheters, or are you trying to introduce the concept of 'safe' include your secondary objectives of admissions, or urethral trauma, stone fromation etc. at the same time, which would be statistically problematic?
Authors’ response: At first, the primary objective is to determine that the incidence of symptomatic UTIs in study participants on the reusable catheters is not significantly higher than study participants who use single use intermittent catheters (maximum of 11% difference is deemed clinically acceptable). Other secondary outcomes are also used to investigate the safe use of the reusable catheters but are not included in the primary outcome/objective. The secondary safety outcomes are: the amount of hospitalization due to a sUTI, bacteremic UTI, urethral damage leading to clinical significant strictures, clinical significant kidney- and/or bladder stone formation and episodes of macroscopic hematuria. We have clarified this in the protocol under the paragraphs ‘Primary outcome measure’ and Secondary outcome measures’.

21) Are UTIs to be based on use of a dipstick / slide assessment of urine?
Authors’ response: Our apologies if our definition of a sUTI was not clear. In our protocol a symptomatic UTI is defined as clinical signs and symptoms of a UTI with the presence of bacteriuria. We choose to define bacteriuria by a positive nitrite test, positive dipslide, positive urine sediment or a positive urine culture. Study participants may consult their general practitioner during the study follow-up and these different diagnostic tests are used by general practitioners to diagnose bacteriuria/sUTI. During the follow-up visits, we will assess any clinical signs and symptoms of the study participants and we will request the results of any diagnostic tests performed at the hospital or at the general practitioner. On the basis of this, we assess whether the study participants have undergone a sUTI as defined in our protocol. We have clarified our definition of a sUTI under the paragraph: ‘Primary outcome measure’.

22) Is there allowance for definition of the UTI site - cystitis vs pyelonephritis, What is to happen if subject has prostatitis or epididymitis? Do these count?
Authors’ response: Yes, distinctive symptoms are registered for pyelonephritis, prostatitis or epididymitis.

23) With blood stream infections, does the urinary pathogen have to match between the blood and urine to definine the source as the urinary tract?
Authors' response: The definition of a bacteremic UTI in our trial is the following: a sUTI and a blood culture positive for a known uropathogen, providing that their urine culture matches the positive blood culture (in case a urine culture was taken before receiving antibiotics). Patients with a positive blood culture and with signs of a UTI, but in absence of a urine culture (as some GPs only use a dipslide/dipstick before they starts antibiotics), will be registered as a bacteremic UTI.

24) A chart of the subject visits and procedures at each visit would be useful to provide a clear timeline for the study protocol.
Authors' response: thank you for this advice. The timeline can be viewed in figure 1.

25) What happens if a subject is admitted to another hospital (outside of the study centers for example) and diagnosed with a UTI that does NOT meet study criteria?
Authors' response: during the follow-up, study participants will be asked if they had symptoms of a urinary tract infection and if they received treatment for this. In case the symptoms does not meet our study criteria, we will not register it as a sUTI, but we will register it as an adverse event related to a specific study arm. All adverse events are classified according to the Common Terminology Criteria for Adverse Events of the U.S. Institutes of Health. Hospitalization is always registered as grade 3 or higher (serious adverse event). We have added this information (including reference) to the paragraph: 'Monitoring'.

26) What happens if a subject has a significant complication e.g sepsis from an obstructing upper tract stone, and has an indwelling urinary catheter placed for monitoring / treatment?
Authors' response: The complication is registered as a serious adverse event and will be treated in the best possible way. When the serious adverse event is over, the patient will (in consent) return to the original study arm to complete the study. If a study participant no longer requires or is no longer able to safely self-catheterize, study participation will be terminated and registered as a dropout.

27) Similar to 25 & 26 in the case of new onset urethral false passage or stricture formation.
Authors' response: If a study participant is no longer able to safely self-catheterize due to a stricture or false passage, study participation will be terminated and registered as a dropout. The urethral stricture / false passage will be registered as an adverse event and will be followed in time until the problem has been solved.

29) Similar to above - what happens in situation where patient is admitted to hospital or has a significant other non-urological emergency?
Authors' response: if a study participant has a non-urological emergency (with our without an admission), it is registered as an adverse event not related to a specific study arm.

30) The Qol questionnaires: Please provide references to the Dutch language validation studies and acknowledgement that the relevant propriatory permissions have been obtained. The referee assumes the questionnaires will be administered in the Dutch language, if not please so state (and in what language they will be administered).
Authors' response: all questionnaires are validated in Dutch and permission is obtained. We have updated the reference list for all Dutch language validation studies.

31) Is there an independent data montioring group / board? If so, how often will they meet and will they be provided with regular updates of the study progression?
Authors' response: This trial is monitored by an independent monitor of the Erasmus MC clinical trial

center. We have uploaded the monitoring plan as an supplementary file.
This trial is assessed by the independent medical ethical committee of the Erasmus MC as a trial with low risk of serious adverse events. In case of a low-risk trial, no monitoring of an independent data safety monitoring board is obligatory. In case of a serious adverse event (grade 3 or more), this will be reported to the testing authorities. At present (inclusion N=103), only one serious adverse event (sUTI treated with intravenous antibiotics, control group) is registered and reported to the testing authorities. The testing authorities are in control to decide if an early interim analysis is needed to ensure the safety of this trial. We have added this information to the protocol under paragraph 'Monitoring'.

32) How will the data collection be managemed? Paper CRF's or an online CRF?
Authors' response: all data will be collected online in pre-designed CRFs.

33) How will the collected data be monitored for completeness and what will be the process for obtainining incomplete data (and the relevant timeline)
Authors' response: all data collection (including completeness, and verifying source documentation) will be monitored by an independent monitor of the clinical trial center. For more information about the monitoring, see the attached monitoring plan.

34) How will the study process statistically incomplete data?
Authors' response: we strive to have no missing values for our outcome measures, specifically for our first outcome measure and our baseline characteristics. Our pre-designed online CRF system is built to minimize this.

35) What are the expected limitations or possible problems of the study?
Authors' response: Some of the patients will not want to participate in the study because they are not willing or not able to change catheters (e.g. due to preference or impaired hand function). In addition, we suspect a high dropout rate due to less practical use of the reusable catheter. A 20% dropout rate is included in the sample size calculation.

36) On the trial registration site, the start date is recoreded as 202-01-19, yet the consort checklist the recruitment question is not answered (item 14a) Please explain
Authors' response: Our apologies if the consort checklist was not filled in properly. We have uploaded a new SPIRIT checklist (asked by the editor). The first inclusion was on 20/02/2020.

37) In evaluating the interventional catheter products, this referee could only find these items on Austrialian websites, Are they actually approved in the EU? or widely used in the EU? or just being imported for the study? If so, please state. (It is recognised that the CE mark means the the manufacturing process(es) meet EU standards). If not actually approved for EU use, please advise that the appropriate regulatory paperwork is submitted and approved.
Authors' response: The manufacturer CreateMedic is certified to produce medical devices (up to class 2B) according to the European directives. This certificate is valid until 24th may 2024 and was authorized by SGS Belgium NV, Notified body 1639. All products manufactured by CreateMedic (including the reusable catheters) are covered by this certificate. We have uploaded the CE-certificate and a declaration of conformity for all products listed/produced by CreateMedic as a supplementary file.

38) Does the supplier or manufacturer of any of the study products have any contribution / inlfuence / consultation to this study or study personnel in the broadest sense? If so, please so state, if this is positive, please explain the conflict mitigation process..If not, please so state.
Authors' response: We do not receive any funding from the Japanese manufacturer or Dutch supplier. All catheters are reimbursed by the health care insurance companies in the Netherlands. As a result, the research team is completely independent of the manufacturer and supplier.

39) Are there any stopping points for the study? If there is no data monitoring board, are the investigators going to examine the study data at intermittent defined points for safety so the trial would be stopped if there sre marked differences between the intervention arm vs the control arm of the study. If there is such a review process, please so state, and also specify the study stopping point / criteria.
Authors' response: This trial is assessed as a trial with low risk of serious adverse events. In case of a low-risk trial, no monitoring of an independent data safety monitoring board is obligatory. For more detail, see the answer of question 31.

Reviewer: 3 Dr. Blayne Welk, Western University
Comments to the Author:
The authors have taken on a significant gap in the urologic literature, and aim to conduct a large RCT to determine if there is a difference in single use versus reuse catethers for lower urinary tract dysfunction. This is a well throught out study. A few comments are included below to include some additional important details in this protocol manuscript. A few points below for the authors to consider:

1. Some minor grammatical issues are located throughout the article. For example: Abstract, introduction: …"power is performed" should be "power has been performed". Background, 2nd sentence: needs to be rephrased: Urinary retention or significant urinary retention is due to LUTD, which can be caused by SCI/MS or in some cases it can be idiopathic. Discussion, 1st sentence: "Up to know" should be "Up to now".
Authors' response: Thank you for your comments on the grammatical issues. We have carefully read the manuscript and corrected some additional mistakes.

2. Two of the objectives do not have any associated methodology reported: explore patients perspectives on reuse seems like it should need a brief summary of a qualitative interview process for some participants at the end of the study. Similarly, determine whether urine cultures change seems like it would require a regular urine sample at study start and end, and some discussion of microbiome analysis etc.
Authors' response: We agree with the reviewer that some of the secondary outcomes are not clearly described. We therefore included a table with all objectives and the primary and secondary outcomes (see the updated protocol). Patient perspectives on reuse is measured by the following statements answered by a Likert-scale from 1 -5 (fully agree – fully disagree): 'I feel responsible for the environmental impact due to my catheter use' and 'I feel responsible for the health care costs due to my catheter use'. In addition, all study participants in the intervention group are briefly interviewed about the reusable catheter at the end of the study.
We agree that the fourth objective to determine whether reuse of catheters leads to changes of the urine cultures is debatable. We removed bacteriuria as a secondary outcome, as this is output rather than an outcome. We do assess standard urine cultures at baseline and during the last visit. We have started a pilot study on the urinary microbiome in patients who administer CISC, but this is outside the scope of this study.

3. What catheter type would generally be used by the control population? I would worry that different catheter types (esp with the discussion of a special non-lubricated catheter for the intervention group) may be a cointervention which could decrease the primary/secondary outcomes? If these are special catheters designed to be reused, that should be made clear so that readers understand it is not a study of reuse of regular PVC catheters (which makes the generalizability of the results a bit more challenging to third world countries etc).
Authors' response: Our aim is to compare the reusable catheter to the standard care provided in the Netherlands. All study participants included until now (N=103) use catheters made of PVC with a hydrogel or hydrophilic coating. Allowing for different types of single use catheters may increase

unexplained variation in sUTI in the control arm, and potentially a loss of power. Defining a rigid treatment protocol for the control arm would remove this unexplained variation, but we expect that the ability to recruit patients for the control arm would be much harder. Our aim is to include 456 patients, so we would expect to get a good representation of contemporary clinical practice in The Netherlands. The reusable catheter is specially designed for reuse, this is described in the protocol under the heading: 'Intervention arm'.

4. The SF Qualiveen is designed for the neurogenic population. Is there a plan to validate within non neurogenic CIC users, or conduct analysis of this specifically within the neurogenic subgroup?
Authors' response: We do not have plans to validate this for the non-neurogenic group.

5. How will antibiotic use be adjusted for in the study (ie low dose prophylaxis, multiple courses of antibiotics during which the patient will not be at risk for the primary outcome)?
Authors' response: We will register any antibiotic use (including prophylaxis) of the study participant during follow up. Unfortunately, we were not able to stratify for antibiotic prophylaxis, as the estimated use is too low.

6. Some more details about the collection of the primary outcome would be helpful. This will be critical to the trial success, and one of the hardest things to do in long-term UTI studies. In figure 1, you are only in contact with them every few months by telephone. How do you know when they have a UTI? How will you make sure symptoms are fully documented? How will you ensure that urine cultures are done for all patients, and people aren't treated on spec with antibiotics by non-trial physicians? Are the trial staff on call 24/7 to assess a sUTIs for these patients throughout the trial?
Authors' response: patients receive a bladder diary in which they can keep track of their symptoms. During the follow-up visits, any sUTI will be registered as an adverse event on the basis of this diary. In combination with diagnostic results, which will be requested from laboratories / GPs.

7. Is the analysis going to be per protocol (as is usually done for noninferiority)? I would assume some people with frequent UTIs in the reuse arm will want to switch over to single use, how will their data be analyzed?
Authors' response: All data will be analyzed per-protocol and intention-to-treat. Patients are not allowed to cross-over.

8. How will adverse events be collected? Only if patient reports them, or will there by active screening for them (ie renal and bladder US at the end of the study to assess for stones)?
Authors´ response: Symptoms of adverse events will be actively checked with the study participants during the anamnesis. If necessary, further diagnostics will be performed to confirm this (e.g. cystoscopy in case of symptoms consistent with an urethral stricture).

9. Are patients reimbursed for any expenses/participation in the study? If so this should be specified in the protocol.
Authors' response: study participants are only reimbursed for the travel costs of their clinical study visits. Each visit is compensated with 20 euros. We have added this under the paragraph 'Declarations' .

10. What are the actual/expected start date and estimated end date of the study?
Authors' response: the first inclusion date is 20/02/2020 and the estimated end date is 31/12/2023.

11. The statistical analysis of a non-inferiority trial is a bit more complex, and I think this should be fully described in the statistical methods section. Furthermore, the outcome will be a non-independent, repeated event over time, which adds another layer of complexity that should be addressed.

Authors' response: The incidence of sUTI will be evaluated using a risk difference and 95% CI to determine non-superiority. It is important to stress that the outcome is not a time-to-event related, since we focus on the number of events at the end of the follow-up period.

VERSION 2 – REVIEW

REVIEWER	Lavelle, John Stanford University, Urology
REVIEW RETURNED	23-Dec-2021

GENERAL COMMENTS	This is an important timely trial in regard to intermittent catheterization. Four items: 1) in your authors reply, it was stated that the intermittent catheters that had been stored in the Milton solution, would be rinsed prior to use. Please include this instruction in the manuscript. This move will likely decrease any risk of damage from the sodium hypocholrite solution. 2) Please state that the sodium hypochlorite solution used is the Milton product used in accordance with the manufacturer instructions (it was in the original draft). 3) It is not entirely clear in the manuscript, if a subject has a symptomatic UTI whether a urine culture is obtained in ALL cases at the time of diagnosis. Starting empiric antibiotics is acceptable, with modification based on the culture results. Please state clearly in the maunscript whether this is the case of not. If not, then on what basis are the treatment antibiotics chosen? and also if not, is there a possibiltiy of resistent bacteria leading to recurrent sUTI in the study? is there a standard durtation for the treatment course? Is this different in febrile UTIs? 4) in the table describing the primary and secondary outcomes would 'number of sUTIs'' instead of 'amount of sUTI '' be acceptable to the authors?

REVIEWER	Welk, Blayne Western University
REVIEW RETURNED	02-Jan-2022

GENERAL COMMENTS	Thank you for responding to my comments. One minor point: The data sharing statement usually refers to how study data might be available to other researchers after completion (ie avialable upon reasonable request to senior author, or publically uploaded to XXX datasharing server 6 months after publication of the primary results etc).

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Prof. John Lavelle, Stanford University
Comments to the Author: This is an important timely trial in regard to intermittent catheterization. Four items:
1) in your authors reply, it was stated that the intermittent catheters that had been stored in the Milton solution, would be rinsed prior to use. Please include this instruction in the manuscript. This move will

likely decrease any risk of damage from the sodium hypochlorite solution.
Author's response: We have added the following sentence: 'To reduce the risk of damage from the cleaning solution, the catheter is rinsed with cold tap water prior to each use. Every reusable catheter will be used for two weeks.'
2) Please state that the sodium hypochlorite solution used is the Milton product used in accordance with the manufacturer instructions (it was in the original draft).

Author's response: We have added the following sentence: 'In this trial, Milton fluid (a product of Procter and Gamble) is used to clean and store the catheter.'

3) It is not entirely clear in the manuscript, if a subject has a symptomatic UTI whether a urine culture is obtained in ALL cases at the time of diagnosis. Starting empiric antibiotics is acceptable, with modification based on the culture results. Please state clearly in the maunscript whether this is the case of not. If not, then on what basis are the treatment antibiotics chosen? and also if not, is there a possibiltiy of resistent bacteria leading to recurrent sUTI in the study? is there a standard durtation for the treatment course? Is this different in febrile UTIs?
Author's response: We have added the following sentences to clarify this: 'If a study participant has a symptomatic UTI, a urine culture will be performed. Based on this result, antibiotics will be started. If a study participant has consulted their general practitioner for a symptomatic UTI, it is possible that antibiotics were started empirically or based on the results of a recent urine culture. The diagnosis is then to be decided by the local consultant involved in study.'
4) in the table describing the primary and secondary outcomes would 'number of sUTIs" instead of 'amount of sUTI " be acceptable to the authors?
Author's response: We have changed the text in the table in 'number of sUTIs'.

Reviewer: 3
Dr. Blayne Welk, Western University
Comments to the Author:
Thank you for responding to my comments. One minor point: The data sharing statement usually refers to how study data might be available to other researchers after completion (ie avialable upon reasonable request to senior author, or publically uploaded to XXX datasharing server 6 months after publication of the primary results etc).
Author's response: We have added the following sentence to the data sharing statement: 'After completion of the trial, the datasets generated and/or analysed will be made available from the senior author on reasonable request.'

VERSION 3 – REVIEW

REVIEWER	Lavelle, John Stanford University, Urology
REVIEW RETURNED	20-Mar-2022

GENERAL COMMENTS	No comments on the revisions.